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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/757,781	REDDY ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-14* is/are pending in the application.

4a) Of the above claim(s) *9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The appeal brief filed December 4, 2003 is acknowledged and has been entered, but the finality of the Office action mailed July 2, 2003 has been withdrawn to set forth additional grounds of rejection herein.

2. Claims 1 and 3-14 are pending in the application. Claims 9-14 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in Paper Nos. 8 and 10.

3. Claims 1 and 3-8 are currently under prosecution.

Claim Rejections - 35 USC § 101

4. Claims 7 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 7 is drawn to a host cell comprising the vector of claim 6. The claim is broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Thus, the claim encompasses host cells that have been transfected with the vector of claim 6 that are comprised within a transgenic animal, including a human.

MPEP § 2105 [R-1] states:

> If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter.

Support for this interpretation of the claim can be found in the specification at page 25, for example.

Amending claim 7 to recite "isolated" before "host cell" can obviate this ground of rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a cDNA molecule, or complement thereof, encoding "a naturally occurring variant" of SEQ ID NO: 2. Claim 4 is drawn to a cDNA molecule, which is "a naturally occurring variant" of SEQ ID NO: 20. Thus, claim 1 is drawn to a genus of nucleic acid molecules that occur in nature and encode structurally different proteins; and claim 4 is drawn to a genus of structurally different nucleic acid molecules occurring in nature, which do not necessarily encode the same protein. Applicant has described only one member of the claimed genus of cDNA molecules, namely the cDNA molecule of SEQ ID NO: 20, which encodes the polypeptide of SEQ ID NO: 2. The written description set forth in Applicant's specification of the claimed genus of cDNA molecules is inadequate and fails to meet the written description requirement set forth under 35 USC § 112, first paragraph, because even given benefit of Applicant's disclosure, the skilled artisan could not immediately envisage, recognize, or distinguish at least a substantial number of members of the claimed genus of naturally occurring cDNA molecules from other cDNA molecules, which are not naturally occurring. The reason the skilled artisan could not immediately envisage, recognize, or distinguish at least a substantial number of members of the claimed genus of naturally occurring cDNA molecules from others is, Applicant has not described the actual structures of every member of the claimed genus, nor has Applicant described a representative number of the members of the claimed genus by describing a characteristic or particularly identifying feature of a naturally occurring cDNA molecule, or a naturally

occurring variant of the polypeptide of SEQ ID NO: 2 encoded by a cDNA molecule encompassed by the claims that is shared by at least a substantial number of the members of the claimed genus, which would allow the skilled artisan to immediately envisage, recognize, or distinguish at least a substantial number of the members from other cDNA molecules not encompassed by the claims. There is no characteristic or particularly identifying feature of a naturally occurring cDNA molecule, or a naturally occurring variant of the polypeptide. Therefore, absent a complete description of the genus and all of its members, most of which have yet to be discovered and described, the skilled artisan could not know whether any given cDNA molecule is naturally occurring, or encompassed by the claims, and would not reasonably accept the assertion that Applicant had possession of the claimed invention at the time the application was filed.

Given its broadest reasonable interpretation, claim 3 is drawn to a cDNA molecule, or complement thereof, encoding a protein having an specific antigenic epitope of SEQ ID NO: 2. Thus, claim 3 is drawn to a genus of nucleic acid molecules encoding structurally different proteins, which are only similar in that they comprise an antigenic epitope of SEQ ID NO: 2, namely the amino acid sequence of SEQ ID NO: 2 spanning the residues at positions 189 and 236. The members of the claimed genus are reasonably expected to differ markedly in structure and function. Applicant has described only one member of the claimed genus of cDNA molecules, namely the cDNA molecule of SEQ ID NO: 20, which encodes the polypeptide of SEQ ID NO: 2. Applicant has not described any specific or particularly identifying function that is shared by polypeptides comprising the recited antigenic epitope. As established by the previous Office action, it would be unreasonable to expect any protein having the recited antigenic epitope to be functionally similar to the polypeptide of SEQ ID NO: 2, because one skilled in the art cannot predict whether a protein having an amino acid sequence that is 95% identical to SEQ ID NO: 2 has a function that is the same or similar to the function of the polypeptide of SEQ ID NO: 2, much less a protein having only the recited antigenic epitope of SEQ ID NO: 2. The written description set forth in Applicant's specification of the claimed genus of cDNA molecules is inadequate and

fails to meet the written description requirement set forth under 35 USC § 112, first paragraph, because even given benefit of Applicant's disclosure, the skilled artisan could not immediately envisage, recognize, or distinguish at least a substantial number of members of the claimed genus of cDNA molecules from other cDNA molecules encoding proteins having the recited antigenic epitope but which differ from SEQ ID NO: 20. The reason the skilled artisan could not immediately envisage, recognize, or distinguish at least a substantial number of members of the claimed genus of cDNA molecules from others is, Applicant has not described the actual structures of at least a substantial number of members of the claimed genus, nor has Applicant described a representative number of the members of the claimed genus by describing a characteristic or particularly identifying feature of SEQ ID NO: 20, or of the polypeptide encoded thereby, that is shared by at least a substantial number of the members of the claimed genus, which would allow the skilled artisan to immediately envisage, recognize, or distinguish at least a substantial number of the members, many of which have yet to be discovered or described, from other cDNA molecules encoding structurally different proteins.

Claim 1 is drawn to a cDNA molecule, or the complement thereof, encoding a protein comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 2 but which differs from the polypeptide of SEQ ID NO: 2, whereas claim 4 is drawn to a cDNA molecule having a polynucleotide sequence that is at least 90% identical to SEQ ID NO: 20 but which differs from the cDNA molecule of SEQ ID NO: 20. Thus, claim 1 is drawn to a genus of nucleic acid molecules encoding structurally different proteins; and claim 4 is drawn to a genus of structurally different nucleic acid molecules, which do not necessarily encode the same protein. Applicant has described only one member of the claimed genus of cDNA molecules, namely the cDNA molecule of SEQ ID NO: 20, which encodes the polypeptide of SEQ ID NO: 2. The written description set forth in Applicant's specification of the claimed genus of cDNA molecules is inadequate and fails to meet the written description requirement set forth under 35 USC § 112, first paragraph, because even given benefit of Applicant's disclosure, the skilled artisan could not immediately envisage, recognize, or distinguish at least a substantial number

of members of the claimed genus of cDNA molecules from other cDNA molecules encoding proteins having an amino acid sequence, which is at least 90% identical to SEQ ID NO: 20 but which differs from SEQ ID NO: 20. The reason the skilled artisan could not immediately recognize or distinguish at least a substantial number of members of the claimed genus of cDNA molecules from others is, Applicant has not described the actual structures of at least a substantial number of members of the claimed genus, nor has Applicant described a representative number of the members of the claimed genus by describing a characteristic or particularly identifying feature of SEQ ID NO: 20, or of the polypeptide encoded thereby, that is shared by at least a substantial number of the members of the claimed genus, which would allow the skilled artisan to immediately recognize or distinguish at least a substantial number of the members from other cDNA molecules encoding structurally different proteins. The reason the skilled artisan could not immediately envisage at least a substantial number of members of the claimed genus of cDNA molecules from others is, as established by the previous Office action, one skilled in the art cannot predict whether a protein having an amino acid sequence, which is homologous to the amino acid sequence of another protein, will have a function that is the same, or even similar to the function of the other, and moreover Applicant has not described which amino acids of the polypeptide of SEQ ID NO: 2 must be retained, or by which other amino acids the amino acids of SEQ ID NO: 2 can be replaced in the structure of another protein so that the other protein retains the function of the polypeptide of SEQ ID NO: 2.

As stated in the previous Office action, MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the art is an unpredictable art and the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicants were in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicants in the specification; nor have Applicants shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor have Applicants described distinguishing identifying characteristics sufficient to show that Applicants were in possession of the claimed invention at the time the application was filed.

In the appeal brief Applicant has traversed the ground of rejection set forth in the Office action mailed July 2, 2003 arguing the following:

(a) Applicant has stated the basic argument set forth in reply to the Office action mailed December 3, 2002 is reiterated. The specification provides an adequate written description of the claimed variant of SEQ ID NO: 2 in terms of chemical and structural properties of SEQ ID NO: 2. The recitation of functional characteristics shared by at least a substantial number of members of the claimed genus of proteins is not an absolute requirement for fulfilling the written description requirement.

(b) In addition, Applicant has submitted none of the literature cited by the Examiner, which teaches the difficulty of predicting protein function based on homology, suggests that functional homology cannot be inferred by a reasonable probability in this case. Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields high probability of functional homology. At best, the literature cited by the Examiner stands for the proposition that it is difficult to predict the function of a protein based on sequence comparisons.

(c) Applicant has referred to *The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement* (66 FR 1099-1111, January 5, 2001). Accordingly Applicant has contended the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known in the art, because variants of SEQ ID NO: 2 are described, for example, at page 3, lines 6-7, as having an amino acid sequence that is at least 95% identical to the polypeptide of SEQ ID NO: 2, because the specification teaches how cDNA molecules encoding portions of the amino acid sequence set forth as SEQ ID NO: 2 were first identified and isolated to derive the consensus sequence of SEQ ID NO: 2 (page 10, lines 12-22), and because at page 10, line 23, to page 11, line 8, the specification describes potential structural and functional motifs identified in SEQ ID NO: 2, which are similar to those identified in rat ASIP and human ASIP.

(d) The claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. In the instant case, there is no mere reliance upon a description of the functional characteristics of the claimed nucleic acid molecules. By

failing to base the written description inquiry upon what is claimed, the Office has failed to provide a proper analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

(e) Brenner et al. provides evidence that the members of the claimed genus of cDNA molecules are not highly variable, so that the description that the members of the claimed genus encode polypeptides that are at least 95% identical to SEQ ID NO: 2 should be regarded as sufficient to describe the invention as required under 35 USC § 112, first paragraph.

(f) The state of the art at the time the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications. The written description inquiry in those cases was based upon the state of the art during "the dark ages" of recombinant DNA technology. Given the remarkable advances made in the technology since the filing of those applications, the skilled artisan given benefit of Applicant's disclosure, would recognize that Applicant was in possession of the claimed invention at the time the application was filed.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

(a) The Examiner reiterates the response to Applicant's arguments, which is set forth in the Office action mailed July 2, 2003 in reply to Applicant's amendment filed February 4, 2003. The written description set forth in Applicant's specification of the claimed genus of cDNA molecules is inadequate and fails to meet the written description requirement set forth under 35 USC § 112, first paragraph, because even given benefit of Applicant's disclosure, the skilled artisan could not immediately envisage, recognize, or distinguish at least a substantial number of members of the claimed genus of cDNA molecules from other cDNA molecules encoding proteins having an amino acid sequence, which is at least 90% identical to SEQ ID NO: 20 but which differs from SEQ ID NO: 20. Accordingly, Applicant's disclosure of the claimed invention would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Applicant has argued the specification provides an adequate written description of the claimed variant of SEQ ID NO: 2 in terms of chemical and structural properties of SEQ ID NO: 2; however, the claims are drawn to a genus of cDNA molecules encoding structurally different proteins. The only member of the claimed genus described by Applicant is the cDNA molecule of SEQ ID NO: 20, which encodes the polypeptide of SEQ ID NO: 2, so Applicant has not met the written description requirement by describing an actual reduction to practice, or by disclosing the structures of at least a substantial number of the members of the claimed genus, and the polypeptide of SEQ ID NO: 2 is not deemed representative of at least a substantial number of members of the claimed genus. The polypeptide of SEQ ID NO: 2 is not deemed representative, because even given Applicant's disclosure of SEQ ID NO: 2, the skilled artisan could not immediately envisage, recognize, or distinguish at least a substantial number of members of the claimed genus of cDNA molecules from other cDNA molecules encoding proteins having an amino acid sequence, which is at least 95% identical to SEQ ID NO: 2 but which differs from SEQ ID NO: 2, because the specification does not describe a characteristic or particularly identifying feature of the polypeptide of SEQ ID NO: 2, which is shared by at least a substantial number of members of the claimed genus, so that the skilled artisan could recognize or distinguish the others proteins encoded by the claimed genus of proteins, which differ structurally from SEQ ID NO: 2.

In reply to Applicant's remark, the recitation of functional characteristics shared by at least a substantial number of members of the claimed genus of proteins is not an absolute requirement for fulfilling the written description requirement, Applicant is correct. As stated in the Office action mailed July 2, 2003 at page 7 and 8, *The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement* (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104).

In reply to Applicant's argument, none of the literature cited by the Examiner suggests functional homology cannot be inferred by a reasonable probability in this case, it is aptly noted Applicant later remarks, at best, the literature cited by the Examiner stands for the proposition that it is difficult to predict the function of a protein based on sequence comparisons alone. The literature establishes that sequence comparisons alone do not yield a reliable inference of a protein's function. Thus, the literature cited by the Examiner supports the Office's position that even given the disclosure of SEQ ID NO: 2, the skilled artisan could not predict, which variant of the polypeptide of SEQ ID NO: 2 having an amino acid sequence that is at least 95% identical to SEQ ID NO: 2, or which are encoded by a cDNA molecule comprising a polynucleotide sequence that is at least 90% identical to SEQ ID NO: 20 would have a function that is the same as, or similar to the function of the polypeptide of SEQ ID NO: 2. If the skilled artisan could predict which cDNA molecules comprising a polynucleotide sequence that is at least 90% identical to SEQ ID NO: 20 encode proteins that are functionally similar or identical to the polypeptide of SEQ ID NO: 2, it follows the skilled artisan cannot envisage, recognize, or distinguish members of the claimed genus and would not be reasonably persuaded that Applicant had possession of the claimed invention at the time the application was filed.

(b) In reply to Applicant's remark, Brenner's basic rule is that sequence homology in excess of 40% over 70 or more amino acid residues yields high probability of functional homology, Brenner et al. discloses the sequence comparisons can yield reasonable inference that proteins are evolutionarily related, or that the genes encoding the proteins have evolved from a common ancestral gene. However, Brenner et al. does not teach sequence comparisons can yield a reasonable inference that two proteins have redundant or even similar functions.

(c) Contrary to Applicant's contention, having described the variants of SEQ ID NO: 2 at page 3, lines 6-7, as having an amino acid sequence that is at least 95% identical to the polypeptide of SEQ ID NO: 2, does not meet the written description standard for reasons that have already been discussed. In particular, Applicant has not met the written description requirement by describing an actual reduction to practice, by

disclosing the structures of at least a substantial number of the members of the claimed genus, or by describing a member of the claimed genus of cDNA molecules, which is representative of at least a substantial number of the members.

Contrary to Applicant's contention, although the specification teaches how cDNA molecules encoding portions of the amino acid sequence set forth as SEQ ID NO: 2 were first identified and isolated to derive the consensus sequence of SEQ ID NO: 2 (page 10, lines 12-22), this disclosure does not suffice to meet the written description standard. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Moreover, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

Contrary to Applicant's contention, the disclosure at page 10, line 23, to page 11, line 8, which describes *potential* structural and functional motifs identified in SEQ ID NO: 2, which are *similar* to those identified in rat ASIP and human ASIP, would not reasonably convey to the skilled artisan that Applicant had possession of at least a substantial number of the claimed cDNA molecules, which are variants of the cDNA molecule of SEQ ID NO: 20 or which encode variants of the polypeptide of SEQ ID NO: 2. At pages 10-11, the specification discloses the amino acid sequence set forth as SEQ ID NO: 2 includes ten *potential* N-glycosylation sites, six *potential* cyclic AMP- or cyclic GMP-dependent protein kinase phosphorylation sites, thirty-four *potential* casein kinase II phosphorylation sites, twenty-six *potential* protein kinase C phosphorylation sites, six *potential* tyrosine kinase phosphorylation sites, two *potential* ATP/GTP-binding sites, regions that are *similar* to PDZ domains, and a region that is *similar* to a aPCK binding region of rat and human ASIPs. However, these disclosures would not reasonably convey to the skilled artisan that Applicant had possession of at least a

substantial number of the claimed cDNA molecules, which are variants of the cDNA molecule of SEQ ID NO: 20 or which encode variants of the polypeptide of SEQ ID NO: 2, because the disclosure are descriptive of potential structural and functional motifs identified in the polypeptide of SEQ ID NO: 2, but are not descriptive of the variants of SEQ ID NO: 2, which are encoded by the claimed cDNA molecules. The presence of any one or more of these potential sites has not been correlated with any particular functional feature that is common to at least a substantial number of the members of the genus of variants encoded by the claimed cDNA molecules. Even if the variants of SEQ ID NO: 2 share these *potential* structural and functional motifs, it is unreasonable to expect the skilled artisan could immediately recognize or distinguish the variants, which are encompassed by the claims, from others, because the skilled artisan would not know which, if any of these potential sites are associated with the actual function of the variants encompassed by the claims. In addition, the mere presence of a tyrosine kinase phosphorylation site, for example, in a protein is not a particularly identifying feature of the protein, because the genus of proteins having such sites is very large, its members have markedly different structures and functions, and the protein tyrosine kinases that phosphorylate its members have widely varying structures and functions.

(d) Contrary to Applicant's contention, the Office has not failed to provide a proper analysis of the present claims; nor has the Office failed to base the written description inquiry upon "whatever is now claimed". The claims are drawn to variants of the disclosed cDNA molecule of SEQ ID NO: 20, which encode variants of the disclosed polypeptide of SEQ ID NO: 2 encoded by SEQ ID NO: 20. Although Applicant has described methods for isolating the claimed variants, which are naturally occurring, Applicant has not described any of variants of the polypeptide of SEQ ID NO: 2 in sufficient detail to allow the skilled artisan to recognize that Applicant had in their possession "whatever is now claimed". Merely reciting that the variants have an amino acid sequence that is at least 90% identical to SEQ ID NO: 20, or encode a polypeptide that has an amino acid sequence, which is at least 95% identical to SEQ ID NO: 2 would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention, because the polypeptide of SEQ ID NO: 2 is not representative of the

genus of variants encoded by the claimed cDNA molecules. Accordingly, the issues raised by the claims of the subject application are *not* fundamentally different from those considered by the Court in deciding *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In those instances, the Court found that the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel* at 1606.

It is duly noted the Examiner did not cite *Lilly* in a prior Office action; nonetheless, contrary to Applicant's assertions, the issues raised by the claims considered by the Court in deciding *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are *not* fundamentally different from the issues that have been raised by the claims in this application. In deciding *Lilly*, the Court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. In this instance, Applicant has not described the functional activity of the polypeptide of SEQ ID NO: 2 or any variant thereof, naturally occurring or not; nor do the claims recite a functional characteristic that is common among members of the claimed genus. Even so, the Court indicated, an applicant is not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a *representative* number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. The Court decided an adequate written description of a DNA molecule requires a precise definition, such as by structure, formula, chemical name, or physical properties - not a mere wish or plan for obtaining the claimed chemical invention. In this instance, Applicant has not disclosed every species encompassed by the genus, but nor has Applicant achieved an adequate written description by disclosing the nucleotide sequences of a *representative* number of DNA molecules falling within the scope of the claimed genus, which have a polynucleotide sequence that is at least 90% identical to SEQ ID NO: 20 encoding variants of SEQ ID NO: 2, which have a functional attribute correlating with the presence of the recited structural feature.

(e) Contrary to Applicants' assertions, the disclosure of Brenner et al. does not appear to support the argument that the members of the claimed genus of cDNA molecules are not highly variable. According to Applicants' argument: "Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with >90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues" (Paper No. 12, page 11, paragraph 3). However, establishing that two polypeptides are evolutionarily related would not establish that a polypeptide, which is at least 95% identical to another but nonetheless different, will bear the same structure or function as the other; and Brenner et al. does not appear to teach otherwise.

In further reply to Applicants' apparent argument that 30% identity is a reliable threshold for establishing functional correlations between structurally similar proteins, As stated in the Office action mailed July 2, 2003, Skolnick et al. (*Trends in Biotechnology* **18**: 34-39, 2000) discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*).

(f) Contrary to Applicant's assertion, even given the remarkable advances made in the technology since the filing of those applications, the skilled artisan given only benefit of Applicant's disclosure could not recognize that Applicant was in possession of the claimed invention at the time the application was filed. This position is supported by the teachings of Skolnick et al., for example, which was published in the year 2000 during the ongoing relatively "enlightened age" of recombinant DNA technology, for reasons already discussed.

7. Claims 1 and 4-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 4 recite the terms "a naturally occurring variant of [...] SEQ ID NO:2" and "a naturally occurring variant of [...] SEQ ID NO:20", respectively. However, there does not appear to be proper and sufficient antecedent basis in the specification for recitation of these terms in the claims. Therefore, recitation of the terms in the claims appears to introduce new matter and thereby violates the written description requirement set under 35 USC § 112, first paragraph.

In the appeal brief Applicant has traversed this ground of rejection again arguing that adequate written support for the recitation of the limitation "naturally occurring" in the claims can be found in the specification. In addition, Applicant has remarked, explicit support for the terms "naturally occurring" and "variant" is found in the specification, so the combination of the terms in the term "naturally occurring variant" in the claims would be understood by one skilled in the art as referring to a variant of SEQ ID NO: 20, or a variant of SEQ ID NO: 2, which occurs in nature. Apparently, Applicant has asserted the ability to combine the terms shows Applicant was in possession of such variant at the time the application was filed.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The fact that the term "naturally occurring variants" of SEQ ID NO: 2 or SEQ ID NO: 20 would be understood as referring to a variant of SEQ ID NO: 20, or a variant of SEQ ID NO: 2, which occurs in nature, is not disputed. However, the mere fact that the terminology is recited in the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed "naturally occurring variants" of SEQ ID NO: 2 or SEQ ID NO: 20. While the terms "naturally occurring" and "variant" appear in the specification, the terms are not used in the context of describing the claimed "naturally occurring variants" of SEQ ID NO: 2 or SEQ ID NO: 20. As stated in the previous Office action, the disclosure at page 7, refers to derivatives of naturally occurring molecules, but does not provide explicit or implicit support for the recitation of the limitation "naturally occurring variant" in the claims. The disclosure at page 12

states, "as a result of the degeneracy of the genetic code, a multitude of cDNA encoding ARP, some bearing minimal similarity to the cDNAs of any known and naturally occurring gene, may be produced" (lines 39-41); thus, this disclosure also does not provide the necessary antecedent basis. Finally, the disclosure at page 13 refers to possible variations in the structure of a cDNA molecule encoding a polypeptide, which could be *made* by selecting combinations based on possible codon choices in accordance with the standard triplet genetic code as applied to the polynucleotide encoding naturally occurring ARP. Accordingly, the disclosure at page 13 does not provide antecedence for the recitation of the limitation of "naturally occurring variant" in the claims.

8. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an isolated host cell comprising the vector of claim 6, does not reasonably provide enablement for any host cell comprising the vector of claim 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 7 is drawn to a host cell comprising the vector of claim 6. The claim is broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Thus, the claim encompasses host cells that have been transfected with the vector of claim 6 that are comprised within a transgenic animal, including nonhuman or human animals and animals treated using gene therapy.

Support for this interpretation of the claim can be found in the specification; see, e.g., pages 21 to 22; and page 25.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to have a reasonable expectation of success in making and using the claimed invention without the need to perform additional, and an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized

in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification does not provide a sufficient amount of guidance, direction, or exemplification to enable the skilled artisan to make or use host cells that are comprised within a non-human transgenic animal. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. Houdebine (*Journal of Biotechnology* 1994, 34: 269-287) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions. Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable. Therefore, it is concluded that one of skill in the art would need to perform undue experimentation in order to make and use the claimed host comprised within a transgenic animal.

Additionally, the specification does not teach provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to have a reasonable expectation of successfully producing host cells within a living organism, which comprise the vectors of claim 6, by gene transfer, or *gene therapy*. The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without need of performing an undue amount of experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teach

that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teach that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies. In addition, Amalfitano et al. discuss numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teach the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself.

It is noted that Amalfitano et al. teach that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction. However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a reasonable expectation of success without need to perform additional experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134) in the abstract. Pandha et al. teach:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues.

In view of the preponderance of evidence establishing the state of the art, now and at the time the application was filed, and the level of unpredictability associated therewith, in the absence of a disclosure of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, it appears that skilled artisan could not make and use the claimed invention with a reasonable expectation of success without having the need to perform an undue amount of experimentation.

Amending claim 7 to recite "isolated" before "host cell" can obviate this ground of rejection.

9. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the claimed invention to produce a protein encoded by the cDNA of claim 1, does not reasonably provide enablement for practicing the claimed invention to produce any protein produced by the host cell of claim 7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims. Moreover, the amount of guidance, direction, and exemplification set forth in the disclosure would be insufficient to enable the skilled artisan to have a reasonable expectation of successfully making and using the claimed invention without having the need to perform an additional and undue amount of experimentation.

The specification provides sufficient guidance, direction and exemplification to enable the skilled artisan to use the claimed method only insofar as the claimed method would be used to produce the protein encoded by the cDNA molecule of claim 1. The host cell produces an enormous number of proteins that are not encoded by the cDNA of claim 1, which could not be produced merely by routine and conventional

extrapolation of Applicant's disclosure. In support of this position, it is duly noted that in Paper No. 12, Applicant stated, "the method of claim 8 can only be used to produce a protein described in claim 1" (Paper No. 12, page 14, paragraph 4).

Amending claim 8 to recite, "encoded by the cDNA of claim 1" after "protein" in line 1 can obviate this ground of rejection.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 4 is rejected under 35 U.S.C. 102(a) as being anticipated by Joberty et al. (*Nature Cell Biology* **2**: 531-539, 2000).

Applicant has traversed the rejection of claim 4 under 35 USC § 102 as being anticipated by Joberty et al., as set herein, or as being anticipated by Izumi et al. or NCI-CGAP, as set forth below, arguing the following:

Having specifically recited "a nucleic acid sequence of SEQ ID NO:20" provides a context that clearly dictates that SEQ ID NO: 20 is the only sequence referred to in the claim.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claim 4 is drawn to a cDNA comprising a sequence of a nucleic acid sequence of SEQ ID NO: 20, or its complement. In examining the novelty of a claim, the claim is given its broadest reasonable interpretation in light of the specification. Contrary to Applicant's assertion, the Examiner's interpretation that claim 4 be read as encompassing a plurality of nucleic acid molecules comprising a polynucleotide

sequence of two or more contiguous nucleotide residues of the polynucleotide sequence set forth as SEQ ID NO: 20 finds support in the specification at page 6, lines 12 and 13. The specification teaches, "the singular forms 'a', 'an', and 'the' include plural reference unless the context clearly dictates otherwise" (specification, page 6, lines 12 and 13). Because the nucleic acid molecule of the prior art comprises one or more sequences of the polynucleotide sequence set forth in SEQ ID NO: 20, the disclosure of the prior art is deemed anticipatory of the claimed invention. Accordingly, also contrary to Applicant's assertion, in light of Applicant's disclosure of the invention, having specifically recited "a nucleic acid sequence of SEQ ID NO:20" does not provide a context that clearly dictates that the claimed cDNA molecule comprise the entirety of SEQ ID NO: 20.

Contrary to Applicant's proposal, in view of the disclosure at page 6, amending claim 4 to recite "the" instead of "a" before "nucleic acid sequence" in line 2 will not obviate these grounds of rejection for the same reasons discussed above. However, amending claim 4 to recite, "comprising the entirety" before "of SEQ ID NO: 20" can obviate the grounds of rejection set forth herein under 35 USC § 102.

12. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Izumi et al. (*Journal of Cell Biology* **143**: 95-106, 1998).

As explained above, Applicant's have traversed this ground of rejection, and although carefully considered, Applicant's arguments have not been found persuasive. Nonetheless, as noted above, amending claim 4 to recite, "comprising the entirety" before "of SEQ ID NO: 20" can obviate this ground of rejection.

13. Claims 4 is rejected under 35 U.S.C. 102(b) as being anticipated by NCI-CGAP (Database GenBank Accession No. AI079538, 1998).

As explained above, Applicant's have traversed this ground of rejection, and although carefully considered, Applicant's arguments have not been found persuasive. Nonetheless, as noted above, amending claim 4 to recite, "comprising the entirety" before "of SEQ ID NO: 20" can obviate this ground of rejection.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 5, 2004

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SUPERVISORY PATENT EXAMINER
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